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The importance of a valid assessment of salt intake in individuals and populations. A scientific statement of the British and Irish Hypertension Society.

Francesco. P. Cappuccio ^{a,b} and Peter S Sever ^c, on behalf of the British and Irish Hypertension Society.

^a University of Warwick, WHO Collaborating Centre for Nutrition, Warwick Medical School, Coventry, United Kingdom

^b University Hospitals Coventry & Warwickshire NHS Trust, Coventry, United Kingdom

^c Imperial College London, National Heart & Lung Institute, United Kingdom.

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Correspondence to:

British and Irish Hypertension Society

c/o In Conference Ltd

Unit 1, Q Court

Quality Street

Edinburgh, EH4 5BP

Tel: +44 (0) 131 336 4203

Email: bihs@in-conference.org.uk

26 **Introduction**

27 High salt[†] intake is a major determinant of blood pressure (BP) in individuals and populations¹. A
28 reduction of salt intake leads to a reduction in BP and is associated with a reduction in the incidence
29 of cardiovascular disease (CVD)¹⁻³. However, in the past few years, some epidemiological studies
30 suggested the presence of a J-shaped association between salt (sodium) consumption and CVD⁴⁻⁸.
31 These results sparked both scientific and media interest and opened a debate on the wisdom of
32 pursuing population-wide salt reduction policies to reduce CVD, as currently recommended by
33 most national and international health organizations, including the World Health Organization
34 (WHO)⁹. Systematic appraisal of these studies identified a variety of pitfalls, suggesting that their
35 results were based on flawed methodologies, including the use of biased methods of assessing salt
36 consumption¹⁰⁻¹¹. The present scientific statement aims to briefly highlight the consequences of
37 such biased estimates of exposure (salt intake) when assessing both individual salt intake (for
38 associations with CVD) and population salt consumption (to evaluate population salt reduction
39 programmes).

41 **Assessment of salt intake.**

42 The 24h urinary excretion of sodium is considered the reference method to assess salt consumption,
43 since approximately 93% of the sodium ingested, mostly as salt[†], is eliminated by the kidney in the
44 next 24h¹². If we ate the same amount of salt every day, a single 24h urine collection would indicate
45 with a high degree of precision how much salt we eat. However, due to the high variability of salt
46 consumption in an individual between days, many more collections on different days would be
47 required to characterize the habitual individual's salt consumption¹³. Therefore multiple
48 assessments are needed, in prospective studies, to obtain a reliable estimate of the degree of
49 association between habitual salt consumption and future risk of CVD^{3,14-16}. To overcome the high
50 methodological burden of collecting complete 24h urine samples in large population-based studies

[†]Salt is sodium chloride – 2.5g of salt contain 1g of sodium.

in some settings, then, alternative easier methods have been proposed. Amongst those alternatives the use of ‘spot’ urine collections and the application of different formulae to derive 24h urinary sodium excretion have become of popular use⁴⁻⁸. The commonest is the Kawasaki¹⁷. This formula relies on urinary creatinine concentration from a spot collection and 24h urinary creatinine excretion predicted from age, sex, height and weight. It is, however, an inappropriate method for estimating salt intake in individuals, due to its unreliability and systematic bias¹⁸. These extrapolations consistently overestimate at lower levels of salt intake and underestimate at higher levels, introducing a systematic bias, detected in all validation studies performed to date, including the PURE Study¹¹ (**Figure 1**).

Consequences of estimating ‘individual’ sodium excretion in associations studies between salt intake and CVD.

An accurate and unbiased measurement of ‘individual’ dietary sodium consumption is paramount in etiological epidemiology. In prospective studies, where multiple complete 24h urinary sodium collections have been used to measure exposure to salt consumption, consistent and graded relationships have been described between sodium excretion and health outcomes (CVD and all-cause mortality) in general populations as well as in patients groups^{3, 14-16}. On the contrary, when studies have used the Kawasaki formula, a J-shaped relationship has been obtained⁴⁻⁸. Finally, when a head-to-head comparison was carried out between measures of salt consumption obtained from repeated 24h urine collections compared to a spot urine, in the prospective assessment of salt and mortality, there was a graded relationship when salt consumption was assessed with multiple 24h collections (with no evidence of increased risk at lower levels up to 3g of salt per day) whereas an ‘erroneous’ J-shaped curve was generated when using the Kawasaki formula from spot urines¹⁹. (**Figure 2a**) Therefore ‘spot’ urine collections with the use of the Kawasaki formula are an inappropriate method for studying associations in individuals in prospective studies, and should not be used in the context of prospective assessment of salt consumption as a predictor of health outcomes.

79 **Consequences of estimating ‘population’ average salt consumption in the evaluation of salt**
80 **reduction programmes.**

81 An accurate and unbiased measurement of ‘average’ dietary sodium consumption in population
82 groups is paramount in public health and policy. The knowledge of a reliable estimate of population
83 intake will help public health professionals in several ways. First, it will establish the size of the
84 problem (how much salt does my population eat?). Second, it will provide the gap from set targets
85 (how much do I have to reduce the average salt consumption to achieve WHO targets of 5g per
86 day?). Third, it will help evaluate the intervention in populations by determining changes in
87 average intake over time. Fourth, it will inform health economic evaluations of health impact and
88 motivate continuous political commitment. So, the choice of the right method for measuring salt
89 consumption is equally important in this setting. In a recent study in South Africa, the validity of
90 different formulas – including Kawasaki - applied to spot urine estimates of sodium were tested
91 against 24h urinary sodium measurements. The study showed that these formulas all fall short of
92 an ideal scenario when assessing the presence and size of the bias²¹. In the case of the Kawasaki
93 formula the size of the bias was equivalent to 5.6g of salt²¹. The important implication of these
94 results for policy is that all these formulas introduce a bias with large inaccuracy both in the
95 baseline estimation and, more importantly, they do not enable them to detect smaller changes in
96 population salt consumption over time ensuing from salt reduction programmes. For instance, if
97 spot urines with Kawasaki estimates had been applied to the evaluation of the 8-year UK national
98 salt reduction programme, a detection of 1.4g per day reduction achieved over that period would
99 not have been easy to detect given the presence of a bias three times as large. Therefore, the
100 effectiveness of the population intervention would have been missed, with crucial implications for
101 further investments and commitments towards that public health policy. The real possibility of this
102 scenario has been reported in the recent head-to-head comparison of an evaluation of the
103 effectiveness of a 6-to-24 months salt-substitution programme in China within the framework of a
104 well-controlled randomized clinical trial. Over the time of intervention there was a statistically

105 significant reduction in average sodium consumption of 0.35g per day ($p=0.039$) when assessed by
106 24h urinary sodium excretion. However, when spot urines with Kawasaki equation were used, the
107 change was detected as -0.09g per day ($p=0.569$), a quarter of the real effect (**Figure 2b**). Therefore
108 ‘spot’ urine collections with the use of the Kawasaki formula are an inappropriate method for
109 studying population changes and should not be used in the context of a public health evaluation of
110 the effectiveness of salt reduction programmes.

111

112 **Conclusions**

113 The evidence supporting global actions for a moderate reduction in salt consumption to prevent
114 CVD is strong and new controversial studies, based on flawed methodology, are inappropriate to
115 address the complex associations between salt intake and CVD outcomes and the evaluation of
116 population salt reduction programmes. They should not overturn the ongoing concerted public
117 health action to reduce salt intake globally.

118

119 **Conflicts of Interest**

120 FPC is a technical advisor to the World Health Organization, President and Trustee of the British
121 and Irish Hypertension Society. PSS declares no conflict of interest.

122

123 **References**

- 124 1. Aburto NJ, Ziolkovska A, Hooper L, Elliott P, Cappuccio FP, Meerpohl JJ. Effect of lower
125 sodium intake on health: systematic review and meta-analyses. *Br Med J* 2013; 346: f1326
- 126 2. He FJ, MacGregor GA. Salt reduction lowers cardiovascular risk: meta-analysis of outcome
127 trials. *Lancet* 2011; 378: 380–2.
- 128 3. Cook NR, Appel LJ, Whelton PK. Lower levels of sodium intake and reduced cardiovascular
129 risk. *Circulation* 2014; 129: 981–9
- 130 4. O’Donnell M, Mente A, Rangarajan S et al. Urinary sodium and potassium excretion, mortality,
131 and cardiovascular events. *N Engl J Med* 2014; 371: 612–23.

- 132 5. O'Donnell MJ, Yusuf S, Mente A, Gao P, Mann JF, Teo K, et al. Urinary sodium and
133 potassium excretion and risk of cardiovascular events. *JAMA* 2011; 306: 2229–38.
- 134 6. Mente A, O'Donnell MJ, Rangarajan S, Matthew J, McQueen MJ, Poirier P, et al. Association
135 of urinary sodium and potassium excretion with blood pressure. *N Engl J Med* 2014; 371: 601-
136 11
- 137 7. Mente A, O'Donnell M, Rangarajan S, Dagenais G, Lear S, McQueen M et al. Associations of
138 urinary sodium excretion with cardiovascular events in individuals with and without
139 hypertension: a pooled analysis of data from four studies. *Lancet* 2016; 388: 465-75.
- 140 8. Mente A, O'Donnell M, Rangarajan S, McQueen M, Dagenais G, Wielgoz A, et al. Urinary
141 sodium excretion, blood pressure, cardiovascular disease, and mortality: a community-level
142 prospective epidemiological cohort study. *Lancet* 2018; 392: 496-506.
- 143 9. World Health Organization. Guideline: sodium intake for adults and children. Geneva: World
144 Health Organization; 2012. p. 1–46
- 145 10. Cobb LK, Anderson CA, Elliott P, Hu FB, Liu K, Neaton JD, et al. Methodological issues in
146 cohort studies that relate sodium intake to cardiovascular disease outcomes: a science advisory
147 from the American Heart Association. *Circulation* 2014; 129: 1173-86.
- 148 11. Cappuccio FP, Beer M, Strazzullo P, on behalf of the European Salt Action Network.
149 Population dietary salt reduction and the risk of cardiovascular disease. A scientific statement
150 from the European Salt Action Network. *Nutr Metab Cardiovasc Dis* 2019; 29: 107-14.
- 151 12. Lucko AM, Doktorchick C, Woodward M, Cogswell M, Neal B, Rabi D, et al. Percentage of
152 ingested sodium excreted in 24-hour urine collections: a systematic review and meta-analysis.
153 *J Clin Hypertens* 2018; 20: 1220-9
- 154 13. Lerchl K, Rakova N, Dahlmann A, Rauh M, Goller U, Basner M, et al. Agreement between
155 24-hour salt ingestion and sodium excretion in a controlled environment. *Hypertension* 2015;
156 66: 850-7.

- 157 14. Mills KT, Chen J, Yang W, Appel LJ, Kusek JW, Alper A, et al. Sodium excretion and the
158 risk of cardiovascular disease in patients with chronic kidney disease. *JAMA* 2016; 315: 2200-
159 10.
- 160 15. Cook NR, Appel LJ, Whelton PK. Sodium intake and all-cause mortality over 20 years in the
161 trials of hypertension prevention. *J Am Coll Cardiol* 2016; 68: 1609–17.
- 162 16. Olde Engberink RHG, van den Hoek TC, van Noordenne ND, van den Born BH, Peters-
163 Sengers H, Vogt L. Use of a single baseline versus multiyear 24-hour urine collection for
164 estimation of long-term sodium intake and associated cardiovascular and renal risk. *Circulation*
165 2017; 136: 917-26
- 166 17. Kawasaki T, Itoh K, Uezono K, Sasaki H. A simple method for estimating 24h urinary sodium
167 and potassium excretion from second morning voiding urine specimen in adults. *Clin Exp*
168 *Pharmacol Physiol* 1993; 20: 7-14.
- 169 18. Campbell N. Validation and comparison of three formulae to estimate sodium and potassium
170 excretion from a single-morning fasting urine compared to 24-h measures in 11 countries. *J*
171 *Hypertens* 2014; 32: 2499-500
- 172 19. He FJ, Campbell NRC, Ma Y, MacGregor GA, Cogswell ME, Cook NR. Errors in estimating
173 usual sodium intake by the Kawasaki formula alter its relationship with mortality: implications
174 for public health. *Int J Epidemiol* 2018; 47: 1784-95.
- 175 20. Cappuccio FP. Evaluating population salt reduction programmes worldwide: the risk of cutting
176 corners! *Public Health Nutrition* 2018; 21(12): 2161-3.
- 177 21. Swanepoel B, Schutte AE, Cockeran M, Steyn K, Wentzel-Viljoen E. Monitoring the South
178 African population's salt intake: spot urine v. 24h urine. *Public Health Nutrition* 2018; 21(3):
179 480-8.
- 180 22. Huang L, Woodward M, Stepien S, Tian M, Yin X, Hao Z, et al. Spot urine samples compared
181 with 24-h urine samples for estimating changes in urinary sodium and potassium excretion in
182 the China Salt Substitute and Stroke Study. *Int J Epidemiol* 2018; 47(6): 1811-20.
- 183

184 **Legends to figures**

185

186 **Figure 1.** Validation and comparison of the Kawasaki formula to estimate 24h urinary sodium excretion
187 from a single morning spot urine sample in the PURE Study. On the left it is the validation in 1,083
188 participants from 11 countries[†] and on the right it is the validation in 120 participants from the Shanxi
189 Province of China[#].

190

191 [†] 1083 consecutive individuals attending follow-up clinics over a period of 2-6 months; 87 from India, 153
192 from China and Colombia, 412 from Argentina, Brazil, Malaysia, South Africa, Turkey, 431 from Canada,
193 Sweden, UAE. [#] 120 participants (60 rural and 60 urban) attending either 3-year or 6-year follow-up visit.
194 Re-drawn from Mente A et al. J Hypertens 2014; 32: 1005-15 (left) and Peng Y et al. PLoS ONE 2016;
195 11(2): e0149655 (right).

196

197 **Figure 2a.** Errors in estimating usual sodium intake by the Kawasaki formula alter its relationship
198 with mortality. Head-to-head comparison with 24h urinary sodium excretion. Re-drawn from He FJ et al.
199 Int J Epidemiol 2018; 47: 1784-95.

200

201 **Figure 2b.** Spot urine collections with Kawasaki equation is inadequate to monitor changes in population
202 salt reduction programmes. Head-to-head comparison with 24h urinary sodium excretion. Drawn from
203 Huang L et al. Int J Epidemiol 2018; 47: 1811-20

204

205

206

207

Figure 1

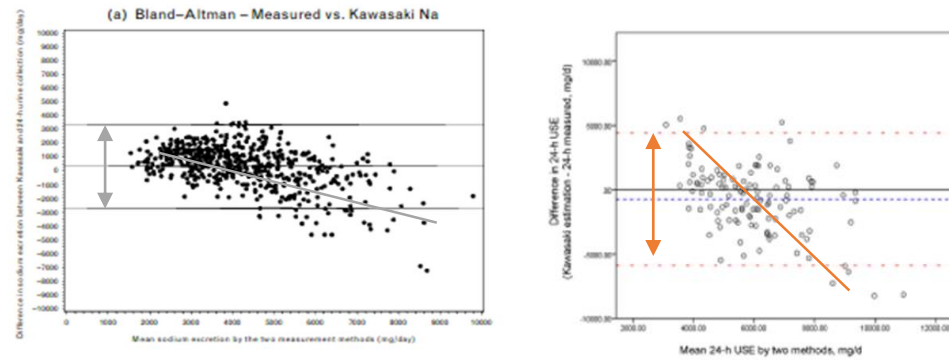
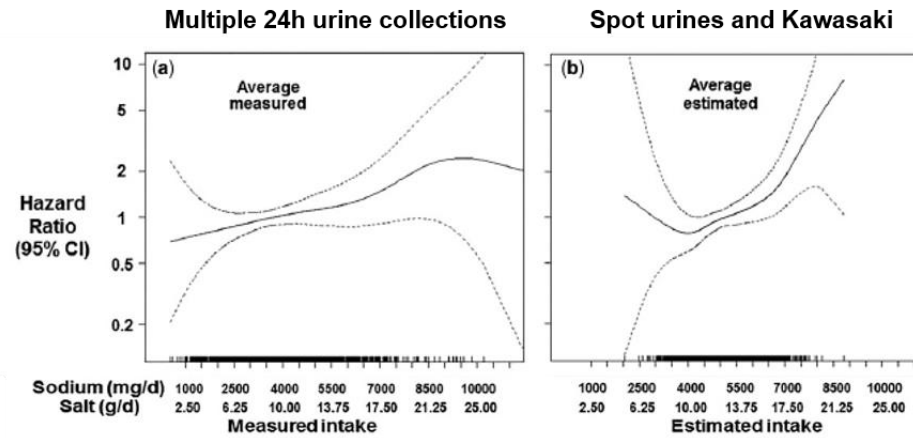


Figure 2

(a)



(b)

